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GH Strongly Affects Serum Concentrations of Mannan-Binding Lectin: Evidence for a New IGF-I Independent Immunomodulatory Effect of GH

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Studies in animals and humans indicate that GH and IGF-I modulate immune function. Recently, it was reported that GH therapy increased the mortality in critically ill patients. The excessive mortality was almost entirely attributable to septic shock or multiorgan failure, suggesting that a GH-induced modulation of immune function was involved. In the present study, we examined whether GH or IGF-I influences the serum concentrations of mannan-binding lectin (MBL). MBL is a plasma protein of the innate immune system that initiates the complement cascade and activates inflammation after binding to carbohydrate structures on microbial surfaces.

We performed a cross-over study of 16 healthy men examined during a control period, and during treatment with either GH or IGF-I for 6 d. The levels of MBL were more than doubled during GH treatment, whereas no changes were observed in the IGF-I group or during the control period ($P < 0.001$). IGF-I levels were elevated similarly during treatment with GH and IGF-I. Subsequently, we studied 30 healthy persons and 25 GH-deficient (GHD) patients randomized to treatment with GH or placebo in a double-blinded manner, and further included samples from 23 patients with active acromegaly examined before and after treatment with octreotide or the GH-receptor antagonist pegvisomant for 3 months. Baseline concentrations of MBL were lower in GHD patients and higher in acromegalic patients than in healthy subjects ($P < 0.02$). Treatment with GH doubled the MBL concentrations in healthy subjects and almost quadrupled the concentrations in GHD patients; whereas in acromegalic patients, the levels of MBL were reduced to approximately two thirds of the initial values during treatment with octreotide or pegvisomant.

Our results demonstrate that treatment with GH, but not IGF-I, significantly increases MBL concentrations. The clinical consequences of this new link between the endocrine and the immune system remain to be elucidated. (*J Clin Endocrinol Metab* 86: 5383–5388, 2001)

HIGH-DOSE GH therapy has recently been reported to increase the mortality rate in critically ill patients (1). The excessive mortality among the GH-treated patients was almost entirely attributable to septic shock or multiorgan failure. The mechanisms underlying these findings remain unexplained, but the investigators suggested that a GH-induced modulation of immune function could be involved. Animal studies have shown that GH administration exerts unfavorable effects on the response to endotoxin-induced sepsis and *Escherichia coli* infections. Many effects of GH are mediated through IGF-I, but no harmful effects were observed when the animals in these studies were treated with IGF-I (2–4).

In contrast to the detrimental effects of GH administration in normal septic animals, GH replacement in hypophysectomized rats actually enhances the resistance to experimental *Salmonella typhimurium* infection (5). So far, no definite clinical symptoms associated with immune dysfunction have been reported in GH-deficient (GHD) humans. However, in a recent prospective study including 1014 hypopituitary patients, a significant increase in the mortality from respiratory infections was observed (6).

Mannan-binding lectin (MBL; also known as Mannose-binding lectin) is an innate immune defense plasma protein synthesized in the liver. It binds to specific repetitive carbohydrate structures on microbial surfaces and subsequently activates the complement cascade through MBL associated serine proteases (MASP-1 and MASP-2) (7, 8), the so-called MBL pathway of complement activation. The concentration of MBL in human plasma is genetically determined. Because of a high incidence of three mutant MBL alleles, as well as mutations in the promoter region of the gene, very large interindividual differences in MBL concentrations exist, and the presence of MBL deficiency among 10% of the population makes it the most frequent immunodeficiency described (9). Several studies indicate that MBL is of importance in first-line immune defense against a number of important pathogens (10–12), and low serum concentrations of MBL are associated with increased susceptibility to recurrent infections (13). However, the high prevalence of the mutant MBL alleles among healthy individuals suggests that MBL deficiency also confers some selective advantages (9). In keeping with this, recent studies indicate that MBL may mediate

Abbreviations: CRP, C-reactive protein; GHD, GH-deficient; MBL, mannan-binding lectin; SIRS, systemic inflammatory response syndrome.

complement activation after hypoxia and thereby potentially aggravate the resulting ischemic injury (14, 15).

To study whether the GH/IGF-I axis is involved in the control of MBL synthesis, we investigated the effect of GH administration on MBL levels in both healthy subjects and GHD patients, in double-blind placebo-controlled designs. Further, we studied the effects of IGF-I administration in healthy subjects and of treatment with octreotide or a GH-receptor antagonist, pegvisomant, in acromegalic patients.

Subjects and Methods

Subjects and experimental design

First, we examined 16 healthy men during a control period and during treatment with either GH (6 IU·m^{-2}, once daily) or IGF-I (50 μg·kg^{-1}, thrice daily), for 6 d, in a cross-over design. The study periods were carried out in random order and separated by a washout period of 4 wk. Blood samples were drawn on d 0, 2, 4, and 6.

Subsequently, 30 healthy subjects (22 males, 8 females) were randomized to treatment with either GH (0.1 or 0.2 IU·kg^{-1}, once daily) or placebo, in a double-blinded manner, for 4 wk. GH or placebo was administered as daily sc self-injections in the evening. To minimize side effects, only 50% of the target dose was given during the first week. Blood samples were drawn on d 0 and 28.

Twenty-five GHD patients (19 males, 6 females) were also studied. GHD was determined as peak GH less than 5 μg/ml at 2 different provocative tests. All patients with other hormonal deficiencies had been on stable substitution with the relevant hormones for at least 1 yr before participation. The patients were randomized to treatment with either GH (2 IU·m^{-2}, once daily) or placebo for 4 months. During the initial 6 wk, the dose of GH (or placebo) was gradually increased to reach target dose. Blood samples were collected at baseline and after 4 months. GH (Norditropin) and placebo preparations were supplied by Novo Nordisk A/S, Copenhagen, Denmark.

Finally, 23 patients with active acromegaly were included. The diagnosis of acromegaly was established on the basis of clinical presentation, evidence of a pituitary adenoma (on computed tomography or magnetic resonance imaging of the pituitary fossa), and elevated serum concentrations of GH and IGF-I. Seven patients were treated with octreotide (50–100 μg sc, thrice daily), and 16 patients were treated with the GH-receptor antagonist pegvisomant (10–20 mg sc, once daily, with a 80-mg loading dose at baseline). Serum was sampled at baseline and after treatment for 3 months.

All blood samples were collected after an overnight fast. The local ethics committees approved the protocols, and all subjects gave written consent to participate.

Analytical methods

Serum MBL concentrations were measured using an in-house time-resolved monoclonal immunofluorometric assay as previously described (16). In brief, microtiter wells were coated with monoclonal anti-MBL antibody (131-I, The State Serum Institute, Copenhagen, Denmark), followed by incubation with diluted samples. After washing, europium-labeled 131-I anti-MBL antibody was added; and, after a second incubation, the binding of labeled antibody was assessed by time-resolved fluorometry (Delphia, Wallac, Inc. Oy, Turku, Finland). Serum total IGF-I was determined after acid-ethanol extraction, using a noncompetitive time-resolved monoclonal immunofluorometric assay (17). Serum concentrations of C-reactive protein (CRP), haptoglobin, and transferrin were measured at the Department of Clinical Biochemistry, Aarhus University Hospital, using standard ultrasensitive latex-enhanced immunotechniques (Cobas Integra 700, Hoffman-LaRoche Inc., Basel, Switzerland).

Statistics

Statistical calculations were done with SPSS for Windows, version 10.0 (SPSS, Inc., Chicago, IL). When comparing MBL levels, Wilcoxon's signed rank test for within-group comparisons, or Mann-Whitney's *U* test or Kruskall-Wallis' test for between-groups comparisons was employed. With all other variables, the paired-samples *t* test or one-way ANOVA was used to evaluate the differences within or between groups. Pearson product moment correlation or Spearman correlation was used to examine the relationships among different variables at baseline and after treatment. P values < 0.05 were considered significant. Because large interindividual differences in serum MBL concentrations exist, changes in MBL levels are expressed as percentages of initial values. All results are expressed as mean ± SE.

Results

Effects of GH and IGF-I on MBL and IGF-I concentrations (Figs. 1 and 2 and Table 1)

During GH treatment of healthy subjects, for 6 d, the levels of MBL were more than doubled. No changes were observed during IGF-I treatment or during the control period (Fig. 1A). IGF-I levels were elevated similarly after treatment with GH and IGF-I (Fig. 1B; d 6, 635 ± 52 *vs.* 680 ± 54 μg/liter, NS). There was no correlation between the increments in MBL and IGF-I during GH treatment.

In Fig. 2, concentrations of MBL at baseline and after treatment of GHD patients and acromegalic patients are depicted. Baseline concentrations of MBL (μg/liter) were lower in GHD patients and higher in acromegalic patients than in healthy subjects (healthy subjects, 1067 ± 147; GHD patients, 754 ± 174; acromegalic patients, 1880 ± 381, $P < 0.02$). In Table 1, changes in MBL and IGF-I concentrations after treatment of healthy subjects or GHD patients with GH, and after treatment of acromegalic patients with octreotide or pegvisomant, are summarized. Treatment with GH more than doubled the MBL concentrations in healthy subjects, with no obvious dose response effect between the two doses of GH used. In GHD patients, MBL concentrations were almost quadrupled during GH treatment; whereas treatment of acromegalic patients, with either octreotide or pegvisomant, reduced MBL levels to approximately two thirds of the initial values. There was no correlation between baseline levels of MBL and IGF-I or between changes in MBL and IGF-I during treatment with GH or octreotide/pegvisomant in any of the groups.

Effects of GH on CRP, haptoglobin, and transferrin concentrations (Table 2)

Baseline serum concentrations of CRP (nM) and haptoglobin (μM) were higher in GHD patients than in healthy subjects (CRP, 33.5 ± 6.4 *vs.* 14.9 ± 3.6, $P < 0.02$; haptoglobin, 12.4 ± 1.2 *vs.* 9.1 ± 0.7, $P < 0.02$). In contrast, baseline values of transferrin (μM) were lower in GHD patients than in healthy subjects (57.7 ± 2.3 *vs.* 65.9 ± 2.5, $P < 0.02$). There was no correlation among baseline levels of MBL, CRP, haptoglobin, and transferrin in either healthy subjects or GHD patients.

Changes in concentrations of CRP, haptoglobin, and transferrin during GH treatment of healthy subjects and GHD patients are summarized in Table 2. There was no correlation among the GH-induced increments in MBL concentrations and changes in CRP, haptoglobin, and transferrin; but a strong inverse correlation between the changes in haptoglobin and transferrin concentrations during GH treatment of GHD patients was observed ($r = -0.80$, $P < 0.01$).

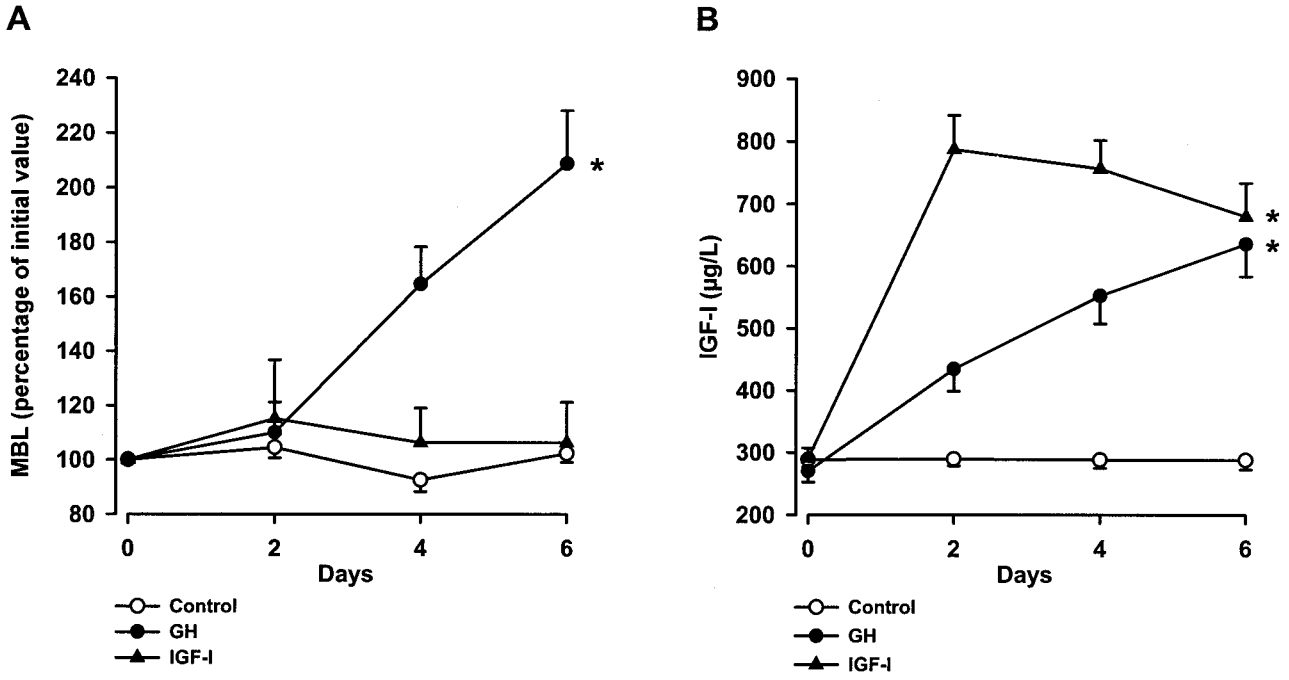

FIG. 1. Effects of GH (6 IU m^{-2}, once daily) and IGF-I (50 μg kg^{-1}, thrice daily) administration on MBL (A) and IGF-I (B) concentrations in healthy subjects. Changes in MBL levels are expressed as percentages of initial values. *, $P < 0.05$ *vs.* control period.

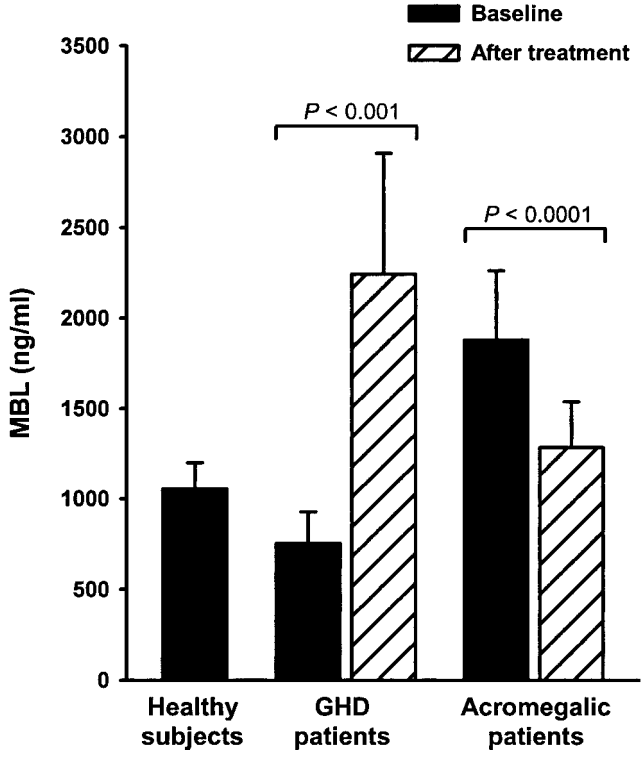

FIG. 2. Mean levels of MBL, at baseline, in healthy subjects, GHD-, and acromegalic patients and after treatment of GHD patients with GH (2 IU m^{-2}, once daily) for 4 months and acromegalic patients with either octreotide (50–100 μg sc, thrice daily) or pegvisomant (10–20 mg sc, once daily) for 3 months.

Discussion

The aim of the present study was to assess the impact of GH and IGF-I administration on the synthesis of MBL. Our results demonstrate that treatment with GH, but not IGF-I, significantly increases MBL concentrations in healthy subjects and GHD patients, suggesting a new link between the endocrine and the immune system. The finding is substantiated by the unequivocal associations between GH status and MBL levels observed in GHD and acromegalic patients. The half-life of circulating MBL, as estimated from infusion studies in MBL-deficient humans, is as long as 5–7 d (18); and it seems most likely that the observed changes in MBL concentrations are attributable to increased synthesis, rather than alterations in the degradation rate. The subjects in the present study were not tested for MBL gene mutations. However, subjects with gene mutations in the MBL allele or in the promoter region of the gene have MBL levels that are clearly in another order of magnitude than those in persons with normal MBL genes (typically 5–50 *vs.* 500-5000 μg/liter), and it was thus possible, indirectly, to estimate the frequency of gene mutations from baseline MBL concentrations. It seemed that the incidence of significant gene mutations was approximately 10% in all groups, but the relative changes in MBL concentrations after treatment with GH, octreotide, or pegvisomant were not correlated to the baseline MBL concentrations (data not shown).

In healthy subjects, we found no dose-response relationship between two different doses of GH and the observed increments in MBL. Because both doses used were in the supraphysiological range, the most likely explanation for the lack of a dose-response effect is that the mechanisms conveying the stimulatory effect of GH on MBL synthesis becomes saturated already at the lower GH dose. From Fig. 1, it seems that the time courses of the stimulatory effects of GH on IGF-I and MBL are very similar. However, there was no correlation between the changes in IGF-I and MBL during treatment of either healthy subjects, GHD-, or acromegalic

TABLE 1. Changes in MBL and IGF-I concentrations after treatment

	Treatment	MBL-levels after treatment		IGF-I concentrations (μg/L)		
		% of initial values	*P*	Before treatment	After treatment	*P*
Healthy subjects	Placebo (n = 11)	101 ± 7	NS	291 ± 16	304 ± 16	NS
	GH low dose (n = 10)	198 ± 16	<0.001[a]	375 ± 41	770 ± 79	<0.001[a]
	GH high dose (n = 9)	201 ± 26	<0.01[a]	299 ± 21	839 ± 94	<0.001[a]
GHD patients	Placebo (n = 13)	129 ± 20	NS	110 ± 17	103 ± 18	NS
	GH (n = 12)	373 ± 99	<0.001[a]	115 ± 18	300 ± 27	<0.001[a]
Acromegalic patients	Octreotide (n = 7)	64 ± 7	<0.05[b]	980 ± 190	407 ± 120	<0.01[b]
	Pegvisomant (n = 16)	69 ± 4	<0.01[b]	733 ± 86	330 ± 34	<0.001[b]

[a] *P* values are changes during treatment *vs.* placebo.
[b] *P* values are values after treatment *vs.* baseline.

TABLE 2. Changes in CRP, haptoglobin, and transferrin concentrations during GH treatment of healthy subjects and GHD patients

Variable	Healthy subjects (change from baseline)				GHD patients (change from baseline)			
	Placebo (n = 10)	GH (n = 15)	Net difference between groups (95% CI)	*P*[a]	Placebo (n = 13)	GH (n = 12)	Net difference between groups (95% CI)	*P*[a]
CRP (nM)	−2.3	−5.3	−3.0 (−16.8 to 10.8)	NS	6.0	−15.0	−21.0 (−46.7 to 4.7)	NS
Haptoglobin (mM)	0.7	−0.1	−0.8 (−3.3 to 1.7)	NS	1.5	−2.3	−3.8 (−6.6 to −1.0)	<0.01
Transferrin (μM)	−2.5	8.9	11.4 (6.1 to 16.8)	<0.001	−2.5	10.3	12.7 (5.7 to 19.8)	<0.001

[a] *P* values are changes during treatment *vs.* placebo.

patients, hence raising the possibility that two different pathways of GH action are involved.

It is well established that low levels of MBL are associated with increased susceptibility to infections (9). However, because of the high frequency of structural gene mutations, large interindividual differences in serum concentrations exist, and no definite cut-off level below which infections occur with increased incidence has been established. Thus, the level for functional deficiency of MBL may vary with different conditions and types of infections. In the present study, GHD patients had lower baseline concentrations of MBL than healthy subjects, and the levels were increased to more than three times the initial values during GH treatment. Until recently, no clear-cut signs of reduced immune function in GHD patients had been observed; but, from a large prospective study of hypopituitary patients, a significant increase in the mortality from respiratory infections was reported (6). Only a very small proportion of the patients in that study received GH replacement, whereas most patients received relevant substitution therapy for other pituitary insufficiencies. In acromegalic patients, we observed significantly increased baseline concentrations of MBL that were almost normalized after treatment with either octreotide or pegvisomant. Stimulation of phagocytosis through opsonization of microorganism with complement fragments is a prominent feature of MBL. In a small study, acromegalic patients had increased phagocytic activity, compared with healthy controls (19); but otherwise, no overactivity of immune function has been reported in acromegalic patients.

The high prevalence of the mutant MBL alleles indicates that some biological disadvantage is associated with increased MBL levels, and it has been hypothesized that high levels of MBL may increase the risk of inflammatory damage (20). The recently reported increased mortality from sepsis and multiorgan failure in GH-treated critically ill patients remains unexplained (1). Systemic inflammatory response syndrome (SIRS) and septic shock are dramatic clinical syndromes that result from uncontrollable invasion of the bloodstream by bacteria or bacterial toxins. Eventually, circulatory insufficiency often develops, leading to widespread organ failure and death. The severity of these conditions depends on the degree of immune activation in the host. A broad range of mediators are involved in the pathogenesis of sepsis, most notably the proinflammatory cytokines IL-1 and TNFα (21). The reported effects of GH on the production of inflammatory cytokines have varied, depending on the experimental conditions. In hypophysectomized rats, treatment with GH increased the endotoxin-induced synthesis of TNFα by macrophages *in vitro* (22). In contrast, treatment with GH decreased the plasma concentrations of IL-1, TNFα, and IL-6 in mice (23) and reduced the cytokine response to endotoxin in calves (24). In rats, GH increased mortality from endotoxin-induced sepsis, without an increased TNFα response (3). *In vitro* treatment of human mononuclear cells with GH inhibited endotoxin-induced production of IL-1 and TNFα (25); and, in a recent study, the proinflammatory cytokine response to endotoxin or surgery in humans was unaffected by high-dose GH therapy (26). As a whole, it seems that GH does not enhance the cytokine response to inflammatory stimuli. MBL is an effective activator of complement and inflammation after binding to a broad array of microorganisms (10); but so far, most studies of MBL have focused on the consequences of MBL deficiency, rather than on the possible role of MBL in the development of SIRS and septic shock. MBL does not normally recognize the body's own tissues (27), but it has recently been reported that cellular hypoxia may alter cell surface glycosylation, leading to increased MBL deposition and complement activation (14). Further, new data indicate that the protease inhibitor aprotinin, which is known to reduce the severity of SIRS and septic shock, selectively blocks the MBL pathway of complement activation, through inhibition of MASP-2, without affecting the classical pathway (28). We found a strong stimulatory effect of GH on MBL synthesis, but the very large variation in MBL levels within the population (from 5 μg/liter to 5 mg/liter) makes it difficult to evaluate the conse-

quences of the observed changes. It seems plausible, however, that increased concentrations of MBL during GH treatment of critically ill patients might disrupt a subtle equilibrium between proinflammatory and antiinflammatory components of the immune system, leading to a detrimental activation of complement and inflammation. The immune system is in a constant balance between efficiently reacting against infectious agents and inflicting injury to the host. It could be hypothesized that, in some individuals (with low MBL levels), GH treatment may raise the MBL levels above a certain threshold of functional deficiency; whereas in others (with high MBL levels), it may induce an untoward overreaction of the immune system.

Most effects of the GH/IGF-I-axis on immune functions have been attributed to IGF-I (29). In the present study, we found no effect of IGF-I administration on the synthesis of MBL, even though the resulting serum levels of IGF-I were comparable with the IGF-I levels obtained during GH administration. In animal experiments, the detrimental effects of GH treatment in septic animals seemed to be IGF-I-independent, because administration of IGF-I in these experiments had no effect, or even improved the outcome (3, 4, 30). In accordance with these findings, IGF-I treatment of critically ill patients with acute renal failure, in a recent placebo-controlled study including 72 patients, did not affect the outcome or mortality (31). The fact that the impact of GH on MBL is IGF-I independent further supports the hypothesis that an exaggerated MBL production could contribute to the detrimental effects of GH in critical illness, inasmuch as IGF-I production is suppressed in this condition.

MBL has been reported to act as an acute phase protein in response to major surgery or malarial infection (32). The increments in MBL under these conditions were somewhat smaller than the changes observed with GH treatment in the present study. To evaluate possible unspecific stimulatory effects of GH on liver protein synthesis, we measured the concentrations of the acute phase proteins CRP and haptoglobin, as well as the constitutive hepatic protein transferrin, during GH treatment of both healthy subjects and GHD patients. The baseline concentrations of CRP were higher in GHD patients, compared with the (unmatched) group of healthy subjects, and tended to decrease during GH treatment. CRP is emerging as a powerful cardiovascular risk marker, and our results are in agreement with a study of long-term GH treatment of GHD men, where GH significantly reduced the CRP levels (33). The haptoglobin levels were also higher in GHD patients than in healthy subjects; and this study is, to our knowledge, the first to report a significant reduction in haptoglobin concentrations during GH treatment of GHD patients. However, similar effects of GH have been observed in rats (34). As in previous studies (35), transferrin concentrations were increased by GH administration in both healthy subjects and GHD patients. There was no correlation between the changes in concentrations of MBL and the other liver proteins; and taken together, these findings indicate that the effects of GH on hepatic protein synthesis are highly differentiated. GH decreased the concentrations of classical acute phase proteins like CRP and haptoglobin, and it seems unlikely that the effects of GH on MBL synthesis are attributable to unspecific stimulation of hepatic protein synthesis.

In summary, we found that GH stimulates the synthesis of MBL via an IGF-I-independent pathway. The clinical consequences of this new link between the endocrine and the immune system remain to be elucidated. As with most components of the immune system, both too-low and too-high levels of MBL may be associated with unfavorable effects. The pathophysiological significance of the present findings should be substantiated by future experimental studies *in vitro* and in animal models, as well as by observational studies in selected critically ill patients.

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